## REMARKS

Review and reconsideration of the Office Action of August 15, 2006, is respectfully requested in view of the above amendments and the following remarks.

No new matter has been added to the claims or the specification.

For the reasons set forth below, Applicants believe that all the claims are now in conditions for allowance.

**Status of the Claims**

Claims 1-5 and 7-22 were pending.

Claim 8, previously reciting "for the preparation of an antimicrobially active pharmaceutical agent", was amended to a method claim.

In order to better quantify the synergistic effect, the discovery of which was the nexus of the present invention, Applicants amend the claims to refer to Kull values, consistent with the specification as filed. Support for the amendment of the claims to refer to Kull value of 1.0 or less can be found in paragraph [00099] of the specification. Support for amendment of claim 2 (Kull value of 0.83 or less) can be found in Table 7 of the specification.

The use of Kull value in claims to quantify level of synergistic effect has been found acceptable by the USPTO, as evidenced by US Patent 6,069,142 wherein the synergistic properties of bactericides were also evaluated by determining the Kull value, or K value. As described in the present specification and the specification of the '142 patent (col 4, lines 44-61), the method for calculating K value is well known to those skilled in the art. In this example, the K value was determined by the following formula:

$$K = \frac{\text{[DOI] In Combination}}{\text{[DOI] Alone}} + \frac{\text{[Towerbrom®] In Combination}}{\text{[Towerbrom®] Alone}}$$

where "[DOI] In Combination" means the concentration of DOI which, when used in combination with Towerbrom®, resulted in inhibition of microbial growth; "[Towerbrom®] In

Combination" means the concentration of Towerbrom® which, when used in combination with DOI, resulted in inhibition of microbial growth; "[DOI] Alone" means the concentration of DOI which, when used alone, resulted in inhibition of microbial growth; and "[Towerbrom®] Alone" means the concentration of the Towerbrom® which, when used alone, resulted in inhibition of microbial growth.

A K value of less than 1 indicates synergy between the two biocides, a K value of greater than 1 indicates antagonism between the two biocides, and a K value equal to 1 indicates an additive effect of the two biocides.

Support for the amendment of claim 11 (further microbial agent does not comprise a straight-chain 1,2-alkanediol) can be found in paragraph [00040] (of application as filed), last two lines.

**Office Action**

Turning now to the Office Action in greater detail, the paragraphing of the Examiner is adopted.

**Claim Rejections – 35 U.S.C. §112**

The Examiner objects to limitations within limitations in claim 5.

Claim 5 is amended to remove the "preferred" limitation.

Withdrawal of the rejections is respectfully requested.

**Claim Rejections – 35 U.S.C. §103**

Claims 1-5,7-19 are rejected under 35 U.S.C. §103 (a) as being obvious over Clarkson et al. (U.S. Patent Application 2001/0036964 A1) in view of Eggensperger et al. (U.S. Patent 5,670,160) and further in view of Riebel et al. ( U.S. Patent Application 2003/0100613A1).

The basic position of the Examiner is that, where the prior art teaches anti-microbial action of alkyldiols, the synergistic effect of combinations of alkyldiols would be obvious.

Applicants respectfully traverse.

As reviewed in detail in paragraphs [00011] – [00020] of the present specification as filed, antimicrobial activity of 5-10 C diols, and combinations of these diols with other antimicrobial agents, has been extensively studied. As explained in paragraph [00021], despite the vast research that has been conducted in this field, it is surprising that straight-chain 1,2-alkanediols with a chain length in the range of 5 to 10 C atoms exhibit a **synergistically intensified** antimicrobial effect, at least against selected germs, if they are combined with a second or further straight-chain 1,2-alkanediols with different chain lengths in the same range.

Applicants acknowledge that

- the claims as filed reciting synergistic effect did not quantify very well the precise degree of synergism, and
- the smaller the step to making the combination, the greater must be the synergism for the combination to be inventive.

Accordingly, Applicants now amend the claims to more precisely quantify the magnitude of the synergistic effect.

The Examiner takes the position that the present claimed combination would be obvious over the combination of teachings of

(1) Clarkson et at teaching 1,2-alkanediols

(2) Cupferman et al disclosing synergistic antimicrobial action in compositions comprising, inter alia, at least one polyol, which may be an 1,2-alkanediol, and a second antimicrobial agent (but not teaching synergistic effects of combinations of different straight-chain 1,2-alkanediols with a chain length in the range of 5 to 10 C atoms).

Obvious to try is not the test, obviousness of results is the test, and there is no suggestion in the combination of cited references leading to the present surprising effects.

Further, Applicants now quantify the synergism in the claims.

Further yet, the method as claimed in claim 8 is not suggested by the cited art.

And further yet, the specific ratios recited in the present claims 20 and 21 are not disclosed in the prior art.

Clarkson is merely illustrative of the state of the art prior to the present invention.

As discussed in the background section of the present specification, in the cosmetic and pharmaceutical industry and also in the food industry there is an ongoing need for agents with antimicrobial properties, in particular for the preservation of perishable products and for the direct cosmetic or therapeutic treatment of microorganisms and particularly those that can give rise to body odor (including underarm and foot odor), acne, mycoses or the like. The search for suitable (active) is difficult because there is no clear dependence between the chemical structure of a substance, on the one hand, and its biological activity towards specific microorganisms (germs) and its stability, on the other hand. Furthermore, there is no predictable relationship between the antimicrobial action, toxicological acceptability, tolerance by the skin and the stability of a substance.

The present invention is based on the surprising finding that straight-chain 1,2-alkanediols with a chain length in the range of 5 to 10 C atoms exhibit a **synergistically intensified** antimicrobial effect, at least against selected germs, if they are combined with a second or further straight-chain 1,2-alkanediols with different chain lengths in the same range.

In particular, it has been found that the mixtures according to the invention of two, three or more straight-chain 1,2-alkanediols of different chain lengths are outstandingly suitable for use for the preservation of articles that would otherwise be perishable.

As discussed in the background section of the specification, and as exemplified by the numerous references discussed therein, experts in the field had already concerned themselves extensively with the antimicrobial properties of 1,2-diols. However, hitherto there has been no indication that **mixtures** of two, three or more straight-chain 1,2-alkanediols, the chain lengths of which (i) are different and (ii) in each case are in the range of 5 to 10 C atoms, possess an antimicrobial action (at least against selected germs) that is **distinctly improved** in the

individual case. The prior art also gave no incentive to use such mixtures (combinations) as antimicrobial active compounds.

In fact, considering the comprehensive research of record on the antimicrobial activity of individual diols having a chain length in the range of 5 to 10 C atoms, it must be see as particularly **surprising** that mixtures of two, three or more straight-chain 1,2-alkanediols, the chain lengths of which (i) are difference and (ii) in each case are in the range of 5 to 10 C atoms display **a strongly synergistic activity and are clearly superior** to the individually dosed 1,2-diols having chain lengths in the same range in the same concentration, in particular with regard to the reduction in germ time. In particular, a CFU value (CFU = number of colony-forming units) of 0 can be achieved in the individual case only with the said mixtures according to the invention.

The mixtures according to the invention develop their synergistic action against a multiplicity of Gram-positive bacteria, Gram-negative bacteria, moulds and yeasts. There is a particularly good action against Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, against yeasts such as *Candida albicans* and against fungi such as *Aspergillus niger*. In this context the very good activity of the 1,2-diol mixtures according to the invention against *Aspergillus niger*, a mould that can be controlled only with very great difficulty, is to be regarded as particularly advantageous, since Applicant's own studies have shown that when individual 1,2-diols with a chain length in the range of 5 to 10 C atoms are used the CFU value thereof cannot be reduced to the value 0.

The present invention also relates to corresponding methods for the cosmetic and/or therapeutic treatment of germs and specifically, in particular, of (a) microorganisms causing body odour, (b) microorganisms causing acne and/or (c) microorganisms causing mycoses, comprising the topical application of the claimed antimicrobially effective amount of a mixture of two, three or more straight-chain 1,2-alkanediols, the chain lengths of which (i) are different and (ii) in each case are in the range of 5 to 10 C atoms, the proportions of the said diols in the mixture being set such that their antimicrobial action is **synergistically intensified**.

As Applicant's own research now showed, the synergistically active mixtures according to the invention consisting of two, three or more straight-chain 1,2-alkanediols, the chain lengths of which (i) are different and (ii) in each case are in the range of 5 to 10 C atoms, not only have a good action against the germs already mentioned above but also against *Staphylococcus epidermidis*, *Brevibacterium epidermidis*, *Propionibacterium acnes* as well as against *Trichophyton* and *Epidermophyton* species, so that they can also be used as agents for the treatment (control) of underarm odour and foot odour and of body odour in general, as agents for the control of acne, as anti-dandruff agents and for the treatment of mycoses (in particular dermatonmycoses.

All areas of the human skin can be infested by mycoses (in particular dermatomycoses and nail mycoses). Areas of the skin on which moisture and warmth can build up as a result of wearing clothing, shoes or jewellery are particularly frequently affected. Fungus diseases of the fingernail and toenail regions are experienced as being particularly unpleasant. Various species of *Trichophyton* and *Epidermophyton* frequently have decisive responsibility for the formation of mycoses. The cosmetics industry is continuously searching for novel agents for the treatment of microorganisms causing these and other mycoses.

The present specification provides extensive evidence of the unexpected strong synergism found with the claimed combinations. See particularly K values in the right column of Table 7.

Table 7:

| MIC values [ppm] for 1,2-hexanediol, 1,2-octanediol and for a C6/C8 diol mixture (2:1) | | | | | |
|---|---|---|---|---|---|
| Determination of the **Synergy Indices (SI)** in accordance with the Kull et al [1,2] equation | | | | | |
| | | | | | |
| Microorganism | Strain No. | MIC C6 | MIC C8 | MIC C6/C8 2:1 | **SI: C6/C8; 2:1** |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| *Staphylococcus epidermidis* | ATCC 12228 | 25000 | 12500 | 6250 | **0.55** |
| *Corynebacterium xerosis* | ATCC 7711 | 12500 | 6250 | 6250 | **0.66** |
| *Brevibacterium epidermidis* | ATCC 35514 | 25000 | 3125 | 6250 | **0.83** |
| *Propionibacterium acnes* | ATCC 11829 | 25000 | 6250 | 3125 | **0.25** |
| *Malassezia furfur* | DSM 6171 | 12500 | 50000 | 50000 | **2.97** |
| *Trichophyton mentagrophytes* | CBS 26379 | 6300 | 1562 | 1562 | **0.49** |
| *Epidermophyton floccosum* | CBS 55384 | 6250 | 3125 | 1562 | **0.32** |
| | | | | | |
| [1] F.C.Kull et al.; Applied Microbiology 9; p. 538-541 (1961) | | | | | |
| [2] D.C.Steinberg; Cosmetics & Toiletries 115 (11); p. 59-62 (2000) | | | | | |

The **SI values clearly show that the 1,2-hexanediol/1,2-octanediol diol mixture has a synergistically intensified activity** and, in addition to its excellent activity as a preservative (cf. Example 1) can also preferentially be used for controlling body odour (SI *Staphylococcus epidermidis*: 0.55; SI *Corynebacterium xerosis*: 0.66; SI *Brevibacterium epidermidis*: 0.83), for controlling acne (SI *Propionibacterium acnes: 0.25)* and for controlling the skin and nail mycoses caused by *Trichophyton* and *Epidermophyton* species (SI *Trichophyton mentagrophytes*: 0.49; SI *Epidermophyton floccosum*: 0.32). On the other hand, in the case of *Malassezia furfur* it was not possible to demonstrate a synergistic effect for the 1,2-hexanediol/1,2-octanediol mixture (SI Malassezia furfur: 2.97, i.e. antagonistic effect).

Accordingly, Applicants have demonstrated the surprising synergistic enhanced antimicrobial activity commensurate in scope with the claims. This synergism is not suggested in Clarkson. The Examiner is also requested to note that there no clear dependence between the chemical structure of a substance, on the one hand, and its biological activity towards specific microorganisms (germs) and its stability, on the other hand. Furthermore, there is no predictable relationship between the antimicrobial action, toxicological acceptability, tolerance by the skin and the stability of a substance. This further supports the unexpected nature of the surprising finding that straight-chain 1,2-alkanediols with a chain length in the range of 5 to 10 C atoms exhibit a **synergistically intensified** antimicrobial effect, at least against selected germs, if they are combined with a second or further straight-chain 1,2-alkanediols with different chain lengths in the same range.

Turning finally to the secondary references, Eggensperger et al and Riebel et al are not cited for teaching combinations of straight-chain 1,2-alkanediols with a chain length in the range of 5 to 10 C atoms, but rather merely the use of supplemental antimicrobial agents.

Accordingly, it is respectfully submitted that the claims as amended are in condition for allowance.

The Commissioner is hereby authorized to charge any additional fees which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account Number 50-0951.

Favorable consideration and early issuance of the Notice of Allowance are respectfully requested. Should further issues remain prior to allowance, the Examiner is respectfully requested to contact the undersigned at the indicated telephone number.

Respectfully submitted,

**Date: February 15, 2007**

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# EXHIBIT B:

# FACSIMILE TRANSMISSION CONFIRMATION

# U.S. Application No. 10/502,132

********** -COMM. JOURNAL- ********** DATE FEB-16-2007 ***** TIME 00:00 ********

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